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Visuospatial dysfunction in Alzheimer's disease and behavioural variant frontotemporal dementia

Shirin Salimi[a], Muireann Irish[b,c], David Foxe[b,c], John R. Hodges[c,d], Olivier Piguet[b,c], James R. Burrell[d,e,*]

[a] Faculty of Medicine, University of New South Wales, Sydney, Australia
[b] The University of Sydney, Brain and Mind Centre and School of Psychology, Sydney, Australia
[c] Australian Research Council Centre of Excellence in Cognition and its Disorders, Sydney, Australia
[d] The University of Sydney, Brain and Mind Centre and Sydney Medical School, Sydney, Australia
[e] Concord Hospital, Sydney, Australia

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ABSTRACT

Objectives: Approximately 30% of Alzheimer's disease (AD) patients are misdiagnosed due to overlapping and evolving clinical features. In particular, the distinction of AD from behavioural variant frontotemporal dementia (bvFTD) can be challenging. Measures of visuospatial ability, which rely on parietal lobe function, show promise as markers of AD as the parietal lobe is preferentially affected early in the disease course. We hypothesise that traditional measures of visuospatial function may help distinguish AD from bvFTD.

Materials & methods: The Addenbrooke's Cognitive Examination (ACE) visuospatial subtask, Rey-Osterrieth Complex Figure (RCF) task, and subtests of the visual object and space perception battery (VOSP) were used to examine visuospatial abilities in 55 AD patients, 51 bvFTD patients, and 54 healthy Controls. A subgroup analysis was performed in patients with Pittsburgh Compound B positron emission tomography (PiB-PET) data.

Results: Relative to Controls, AD and bvFTD patients were impaired on almost all visuospatial tasks. Significantly worse performance was observed in AD relative to bvFTD patients on drawing tasks (ACE pentagons/loops copy, cube copy, and all RCF scores) and tasks of spatial orientation (VOSP cube analysis), when controlling for disease severity.

Conclusions: Visuospatial measures demonstrate limited ability to distinguish between AD and bvFTD unless disease severity is taken into consideration. Controlling for disease severity reveals a disproportionate visuospatial impairment in AD compared to bvFTD. Development of targeted measures of visuospatial function is required to improve differential diagnosis of these syndromes.

1. Introduction

Diagnostic uncertainty is a major challenge in Alzheimer's disease (AD), particularly in atypical presentations, younger-onset patients, and in the setting of non-specialised memory clinics. Indeed, close to 30% of patients diagnosed clinically with AD harbour a different pathology at post-mortem [1]. Many discordant cases have underlying frontotemporal lobar degeneration (FTLD) [1]. Conversely, up to a quarter of cases clinically diagnosed with behavioural variant frontotemporal dementia (bvFTD) show amyloid pathology indicative of AD [2]. As such, overlapping, evolving, and non-specific symptoms lead to diagnostic uncertainty and inaccuracy, despite the recent refinement of diagnostic criteria for AD [3]. Diagnostic ambiguity exacerbates disease burden for patients and families, and complicates recruitment for clinical trials [4,5].

Reliable in vivo predictors of amyloid pathology exist [6], but are often confined to research settings due to cost, accessibility, or patient safety [7]. Neuropsychological tests of episodic memory were traditionally the main focus of efforts to improve AD diagnosis prior to the development of amyloid biomarkers [8–10]. Several recent studies, however, have demonstrated comparable episodic memory profiles across AD and bvFTD [11–14]. Similarly, the use of executive tasks to differentiate bvFTD from AD is problematic, with evidence of executive dysfunction in atypical presentations of AD [15]. The development of specific neuropsychological markers to accurately distinguish atypical AD cases from bvFTD would constitute a significant advance in the

* Corresponding author at: Concord Clinical School, Sydney Medical School, The University of Sydney, Australia.
E-mail address: james.burrell@sydney.edu.au (J.R. Burrell).

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differential diagnosis of dementia.

Parietal lobe involvement occurs early in AD [16–21], yet is uncommon in sporadic cases of bvFTD [22,23] occurring typically only in 10% of cases caused by the *C9orf72* repeat expansion [24,25]. Parietal atrophy may also occur in more advanced bvFTD, even in the absence of a genetic cause [26,27]. Hence, tests of visuospatial abilities, which rely on parietal lobe function [18,28,29], may be useful in distinguishing AD from FTD, at least in the earliest stages of the disease [30–32]. Few studies have investigated the utility of visuospatial tasks in differentiating AD from bvFTD, although cube analysis [33] and clock drawing test [34–36] show promise. Novel computerised tests of topographical memory show most potential [32,37], but are not universally available and may be difficult to administer in busy clinical settings. The question remains whether widely accessible tests of visuospatial abilities can reliably differentiate AD from FTD and, among these tasks, which of these display the greatest diagnostic accuracy.

The present study assessed the diagnostic utility of validated visuospatial tasks commonly used in a clinic setting to determine whether visuospatial impairments are specific to amnestic AD compared to probable bvFTD. We hypothesised that AD would demonstrate greater impairment compared to bvFTD on visuospatial tasks reflecting a core visuospatial deficit in AD.

2. Materials & methods

2.1. Participants

Patients diagnosed with probable amnestic AD or with probable behavioural variant FTD (bvFTD) were recruited from FRONTIER, a younger onset dementia research clinic in Sydney, Australia, from 2007 to 2016. Dementia diagnosis was established via consensus following detailed clinical assessment, formal neuropsychological testing, and structural brain imaging. Patients with AD met clinical criteria for amnestic AD [3]. Briefly, definite and probable AD patients presented with episodic memory dysfunction, impairment in at least one other cognitive domain, and relatively preserved social conduct according to their carer, with associated medial temporal lobe atrophy on imaging as per the McKhann criteria [3]. Patients with diagnoses of corticobasal syndrome [38], logopenic progressive aphasia [39], or posterior cortical atrophy [40] were excluded from the study. Patients with bvFTD met current diagnostic criteria for probable bvFTD [36], presenting with prominent behavioural disturbance characterised by apathy and disinhibition, with impaired social conduct and loss of insight. In keeping with the diagnostic criteria for a probable diagnosis, all bvFTD patients had frontotemporal atrophy on MR imaging, or frontotemporal hypometabolism on fluorodeoxyglucose PET (FDG-PET). CSF analysis was not conducted for this study. Only patients who scored between 50 and 88/100 on the Addenbrooke's Cognitive Examination-Revised or III (ACE-R/ACE-III) [41–43] were included. Patients with significant motor impairments that impeded their ability to perform the basic movements of the neuropsychological testing were excluded from the study.

Healthy Control participants were selected from a database of volunteers. All Control subjects were free of neurological disease at the time of assessment, scored ≥88/100 on the ACE, and performed within normal limits on a standard neuropsychological test battery. Exclusion criteria included prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease, alcohol and other drug abuse, and limited English proficiency. Ethical approval for this study was obtained from the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

2.2. Cognitive testing

As part of the diagnostic workup, cognitive screening was performed using the ACE–R (pre 2014) and ACE-III (2014 onwards) [41,42]. This instrument assesses the integrity of a range of cognitive domains including attention and orientation, memory, verbal fluency (via phonemic and category word generation tasks), language, and visuospatial skills, and is scored out of 100 (higher scores denoting better performance). Performance on the ACE-III correlates highly with performance on the ACE-R [43]. A score below 88/100 is indicative of dementia, a threshold established from a large cohort study providing a sensitivity of 86% and specificity of 95% [41–44]. Dementia severity was measured by the Functional Rating Scale (FRS) [45], a measure of functional impairment. The FRS is based on questions from the Disability Assessment for Dementia functional scale and the Cambridge Behavioural Inventory (CBI), producing a 75-item questionnaire covering behavioural disorders and functional disability. This measure was chosen as other existing dementia severity scales focus on AD symptoms, thus potentially underestimating the progression seen in other dementia syndromes [47]. FRS scores were not available for five AD patients and three bvFTD patients.

Visuospatial function was assessed using the visuospatial subscale of the ACE, the Rey Complex Figure test (RCF) [48], and the visual object space perception battery (VOSP). The VOSP was only completed in a subgroup of patients [49]. The visuospatial component of the ACE-R and ACE-III is identical with the exception of the design copy task where the intersecting pentagons are replaced by intersecting infinity loops [41]. Given the retrospective nature of the study, only data from three spatial subsets of the VOSP were available (dot counting, position discrimination, and cube analysis), and only administered to patients scoring below 30/36 on the RCF copy test due to resource limitations [49]. The dot-counting VOSP subtask requires the patient to count the number of dots in each square without pointing. The position discrimination VOSP subtask asks participants to discriminate between squares with either centred or off-centred dots. The cube analysis VOSP subtask presents a two-dimensional image of several stacked cubes and the patient must determine how many cubes are shown.

2.3. PiB-PET imaging

PiB-PET imaging was developed as a biomarker of amyloid deposition to improve the diagnosis of AD, and a positive PiB-PET is an exclusion criterion for bvFTD [36,50]. PiB-PET scans were conducted on a subset of AD patients as previously described [51]. Briefly, 370 MBq ^{11}C-PiB was given intravenously, with a 30-min acquisition using a Phillips Allegro™ PET camera in 3D mode 40 min later. The neocortical β-amyloid burden was expressed as the average standardised uptake value ratios. A hierarchical cluster analysis on healthy Controls yielded a cut-off for 'high' or 'low' neocortical standardised uptake value ratios of 1.5, consistent with cut-off values used in previous PiB-PET studies [52,53].

2.4. Statistical analysis

Statistical analyses were performed using SPSS 23.0 (IBM Corp). Kolmogorov-Smirnov tests were used to determine suitability of variables for parametric analyses. Normally distributed continuous variables were analysed using ANOVA and post-hoc comparisons were performed using independent sample *t*-tests. The experimental variables (ACE, RCF, and VOSP) were not normally distributed and thus group comparisons were conducted using Kruskal-Wallis tests, followed by pairwise between-group comparisons using Mann-Whitney *U* tests. Participants were matched according to their age, sex, years of education, and patient groups were matched for overall cognitive scores (ACE total). Disease severity, reflected by the FRS score, was entered as a covariate using a multivariate analysis of covariance (MANCOVA),

Table 1
Demographic, clinical and cognitive characteristics in AD, bvFTD and control groups[a].

	AD	bvFTD	Control	Statistic (df)	*p*-value	Post-hoc
Number	55	51	54			
Age[b]	65 (8.1)	62 (7.5)	65.4 (7.7)	5.3 (2)	0.071	–
Male (%)[c]	31 (56.4%)	27 (52.9%)	20 (37%)	4.6 (2)	0.100	–
Education (years)[b]	12 (3.1)	11.47 (2.7)	12.42 (2.6)	4.7 (2)	0.095	–
Disease duration (years)[d]	3.92 (3.1)	4.34 (3.0)		1255.5	0.353	–
FRS score[e]	0.8 (1.5)	−0.69 (1.4)		0.244 (96)	< 0.00001*	bvFTD < AD
ACE-R/ACE-III Total[b,f]	71.1 (9.9)	74.2 (11.2)	94.6 (3.6)	105.1 (2)	< 0.00001*	AD = bvFTD < control
Attention[b]	14.3 (2.6)	15.3 (2.3)	17.6 (1.0)	63.4 (2)	< 0.00001*	AD < bvFTD < control
Memory[b]	13.6 (4.1)	17.5 (5.1)	24.2 (1.9)	95.5 (2)	< 0.00001*	AD < bvFTD < control
Fluency[b]	7.9 (2.7)	5.7 (3.7)	12.2 (1.5)	91.9 (2)	< 0.00001*	bvFTD < AD < control
Language[b]	22.2 (2.9)	21.8 (3.5)	25.1 (1.2)	54.5 (2)	< 0.00001*	AD = bvFTD < control
Visuospatial[b]	13.2 (2.8)	13.9 (2.0)	15.5 (0.8)	36.3 (2)	< 0.00001*	AD = bvFTD < control

Note: Values are mean scores with standard deviations in brackets where appropriate.
Missing scores: FRS Score: 3 bvFTD, 5 AD.
[a] AD = Alzheimer's disease; bvFTD = behavioural variant frontotemporal dementia.
[b] χ^2, [c]*H* (corrected for ties), [d]U value, [e]F value.
[f] ACE-R = Addenbrooke's Cognitive Examination-Revised; ACE-III = Addenbrooke's Cognitive Examination-III.
* indicates the results that were statistically significant.

Table 2
ACE-R/ACE-III, RCF and VOSP performance in AD and bvFTD patients, and healthy controls[a].

Visuospatial task (max score)	AD	bvFTD	Control	Statistic[b] (df)	*p*-value	Post-hoc
ACE-R/ACE-III						
Visuospatial subtotal (16)	13.2 (2.8)	13.9 (2.0)	15.5 (0.8)	36.3 (2)	< 0.0001*	AD = bvFTD < control
Pentagons/loops (1)	0.7 (0.5)	0.9 (0.3)	0.9 (0.2)	18.9 (2)	< 0.0001*	AD < bvFTD = control
Cube (2)	1.2 (0.9)	1.5 (0.8)	1.9 (0.2)	25.9 (2)	< 0.0001*	AD < bvFTD < control
Clock (5)	3.9 (1.3)	3.9 (1.1)	4.7 (0.7)	22.2 (2)	< 0.0001*	AD = bvFTD < control
ACE dot counting (4)	3.5 (0.7)	3.5 (0.9)	3.9 (0.3)	14.0 (2)	0.001*	AD = bvFTD < control
Incomplete letter perception (4)	3.9 (0.4)	4 (0.0)	4 (0.0)	5.8 (2)	0.055	AD = bvFTD = control
RCF						
Copy score (36)	23.4 (10.1)	25.2 (6.9)	32.6 (2.8)	50.8 (2)	< 0.0001*	AD = bvFTD < control
VOSP						
Dot counting (10)	9.3 (1.1)	9.2 (1.4)	9.9 (0.5)	6.2 (2)	0.046*	AD = bvFTD < control
Position discrimination (20)	18.7 (1.7)	18.7 (1.8)	19.8 (0.6)	7.3 (2)	0.027*	AD = bvFTD < control
Cube analysis (10)	6.9 (3.4)	8.1 (2.4)	9.1 (1.7)	8.7 (2)	0.013*	AD = bvFTD < control

Note: Values are mean scores with standard deviations in brackets where appropriate.
VOSP sample size: 38 AD, 38 bvFTD, 17 Controls.
[a] AD = Alzheimer's disease; bvFTD = behavioural variant frontotemporal dementia; ACE-R = Addenbrooke's Cognitive Examination-Revised; ACE-III = Addenbrooke's Cognitive Examination-III; RCF = Rey-Osterrieth Complex Figure; VOSP = Visual Object and Space Perception Battery.
[b] *H* (corrected for ties).
* indicates the results that were statistically significant.

where appropriate. Categorical data were analysed using the Chi-Square test. A *p*-value of < 0.05 was considered significant.

3. Results

3.1. Patient demographics and clinical features

A total of 160 subjects were included in the study: 55 AD and 51 bvFTD patients, and 54 Controls (Table 1). The groups did not differ in terms of age, sex, years of education, and disease duration (all *p* values > .07). Consistent with previous reports [23,54], the bvFTD group was more functionally impaired than the AD group, as measured by the FRS ($p < .0001$). The ACE total score differed significantly across the groups, with post-hoc tests demonstrating impairment in both dementia groups relative to Controls, but there was no significant difference between AD and bvFTD ($p = .207$). On the ACE subscales, AD patients showed characteristic deficits in memory ($U = 1049.0$, $p = .024$) and attention ($U = 782.0$, $p < .0001$) compared with the bvFTD patients and Controls, whereas the bvFTD group displayed impaired verbal fluency ($U = 944.5$, $p = .003$) compared with AD patients and Controls.

The AD and bvFTD subgroups who completed the VOSP (AD = 38; bvFTD = 38; Controls = 17) were age- and sex-matched with Controls within their subpopulation, however Controls who performed the VOSP were significantly older relative to the overall Control cohort ($p = .002$, H (corrected for ties) = 12.5, df = 2). These dementia subgroups were largely representative of the overall cohort, although the bvFTD patients were younger ($U = 144.5$, $p = .026$, mean of 60.6 vs 62 years) and had completed more years in formal education ($U = 141.5$, $p = .027$, mean of 11.97 vs 11.47 years) than the overall bvFTD group. Consistent with the overall cohort, the bvFTD patients were more severely impaired than the AD patients on the FRS ($p < .001$, $F = 13.9$, df = 1, 68).

All groups in the VOSP subpopulation were more impaired on the ACE visuospatial subtotal compared to the whole disease or control group respectively (AD: $U = 180.0$, $p = .008$; bvFTD $U = 113.0$, $p = .003$; Controls $U = 195.0$, $p = .008$). This finding is to be expected given that participants (patients and Controls) only completed the VOSP if they performed poorly on the RCF copy.

3.2. Visuospatial performance

AD patients were consistently impaired across all visuospatial tasks compared to Controls (ACE visuospatial subscale, RCF, and VOSP), with

Table 3
Visuospatial task performance in AD and bvFTD patients controlling for disease severity as indexed by the FRS[a].

Visuospatial task (max score)	AD estimated means	bvFTD estimated means	Statistic (df)	*p*-value
ACE-R/ACE-III[b]				
Visuospatial subtotal (16)	12.8 (0.4)	14.1 (0.4)	5.2 (1, 95)	0.025*
Pentagons/loops (1)	0.6 (0.1)	0.9 (0.06)	14.4 (1, 95)	< 0.001*
Cube (2)	1.0 (0.1)	1.6 (0.1)	9.7 (1, 95)	0.002*
Clock (5)	3.8 (0.2)	3.9 (0.2)	0.24 (1, 95)	0.625
Dot counting (4)	3.5 (0.1)	3.6 (0.1)	0.266 (1, 95)	0.607
Incomplete letter perception (4)	3.9 (0.5)	4.0 (0.5)	3.2 (1, 95)	0.077
RCF[c]				
Copy score (36)	22.0 (1.3)	26.3 (1.4)	4.8 (1, 93)	0.031*
VOSP[d]				
Dot counting (10)	9.1 (0.2)	9.3 (0.2)	0.72 (1, 67)	0.398
Position discrimination (20)	18.5 (0.3)	18.9 (0.3)	0.83 (1, 67)	0.365
Cube analysis (10)	6.5 (0.5)	8.3 (0.5)	5.0 (1, 66)	0.029*

Note: Values are mean scores with standard error of the mean in brackets where appropriate.
Note: All statistics are *H* (corrected for ties) except for [e]F value.
Population size considering missing FRS scores: ACE Population: 50 AD and 48 bvFTD; RCF Population: 49 AD and 47 bvFTD; VOSP Subpopulation: 35 AD and 35 bvFTD, 1 patient missing VOSP cube analysis.
[a] AD = Alzheimer's disease; bvFTD = behavioural variant frontotemporal dementia; FRS = Frontotemporal Dementia Rating Scale. [b]ACE-R = Addenbrooke's Cognitive Examination-Revised; ACE-III = Addenbrooke's Cognitive Examination-III. [c]RCF = Rey-Osterrieth Complex Figure. [d]VOSP = Visual Object and Space Perception Battery.
* indicates the results that were statistically significant.

a trend towards a significant impairment for incomplete letter perception on the ACE (Tables 2 and 3). This pattern of impairment was also evident in the bvFTD group. Specifically, the bvFTD group was impaired on all components of the ACE visuospatial subtask relative to Controls (all p values < .001), with the exception of the pentagon/loops copy (p = .414) and incomplete letter perception (p = 1.000) components. In addition, the bvFTD patients were impaired on the RCF copy and all VOSP tasks (all p values < .02) relative to Controls.

Direct comparison of the patient groups revealed that AD and bvFTD groups performed comparably across the majority of the visuospatial tasks, apart from pentagons/loops copy (U = 1055.5, p = .002, outcomes were consistent across both versions) and cube copy (U = 1131.5, p = .049), where performance was significantly worse in AD relative to bvFTD patients.

3.3. Considering disease severity

The FRS score was used to control for the effect of disease severity, which was greater in bvFTD compared to AD. A MANCOVA, with FRS score included as a covariate, revealed disproportionate visuospatial impairments in AD compared to bvFTD patients (Figs. 1 and 2). Specifically, AD patients were significantly impaired on the ACE visuospatial subtotal, and all constructional tasks (pentagons/loops, cube copy, and RCF) compared with the bvFTD group (all p values < .031; Table 3). In contrast, performance on visuoperceptual tasks, such as dot counting, incomplete letter perception, and position discrimination components of the VOSP, did not differ between AD and bvFTD (all p values > .365) with the exception of the VOSP cube analysis component (p = .029).

3.4. PiB-PET subpopulation results

Thirteen patients from this study underwent a PiB-PET scan. All nine patients with positive PiB-PET imaging had a corresponding clinical diagnosis of AD prior to imaging, whereas the four patients with PiB-PET negative imaging were diagnosed clinically with bvFTD.

4. Discussion

The present study demonstrated that the majority of visuospatial neuropsychological tests typically used in clinical settings do not reliably distinguish AD and bvFTD, unless disease severity is taken into consideration. Development of visuospatial tests, not influenced by executive or motor deficits, are needed to improve diagnostic utility at all disease stages.

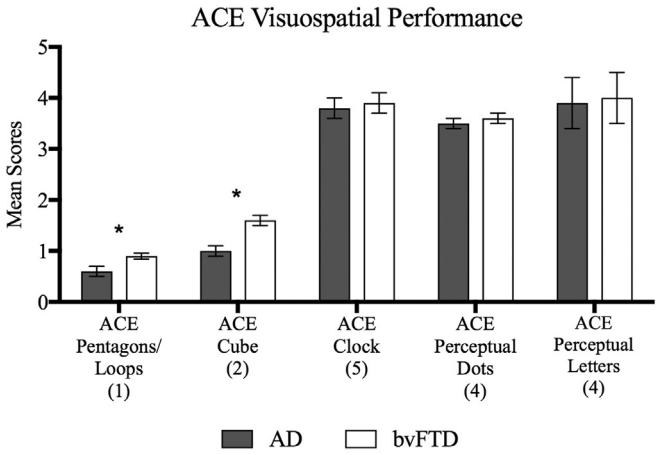

Fig. 1. Performance on Addenbrooke's Cognitive Examination (ACE) visuospatial subcomponents in Alzheimer's disease (AD) versus behavioural variant frontotemporal dementia (bvFTD).
AD patients performed significantly worse than bvFTD patients on the visuospatial subtotal, pentagons/loops and cube copy components of the ACE. *p < .05, **p < .001.

Consistent with previous studies, the AD group was impaired across all tests of visuospatial abilities. A number of studies have reported visuospatial deficits in AD, reflected by impaired performance on the ACE visuospatial subscale [42], RCF copy [13,20,41,55–57] and VOSP dot counting and position discrimination subtasks [58]. As such, our findings support the view that visuospatial dysfunction is a prominent early feature of clinically probable AD [19,31,32].

Counter to our initial predictions, the bvFTD group demonstrated significant, albeit variable, visuospatial impairments relative to Controls. These findings, however, are in keeping with several studies reporting visuospatial deficits in bvFTD compared to Controls on the ACE visuospatial subscale [41] and RCF copy tasks [56,59]. Furthermore, bvFTD and AD patients have shown a similar degree of visuospatial impairment on the ACE visuospatial subtotal [60–62]. These results suggest that performance on commonly used visuospatial tasks is

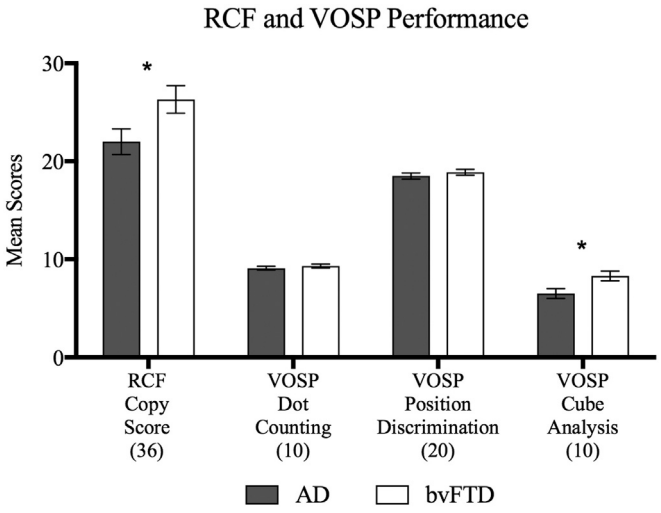

Fig. 2. Rey-Osterrieth Complex Figure (RCF) and visual object and space perception battery (VOSP) performance in Alzheimer's disease (AD) versus behavioural variant frontotemporal dementia (bvFTD).
AD patients performed significantly worse than bvFTD patients on the RCF copy score and VOSP cube analysis. $^{*}p < .05$, $^{**}p < .001$.

influenced by deficits in other cognitive domains and may not be helpful in distinguishing between bvFTD and AD. Ideally, tests of visuospatial ability that do not rely on other cognitive processes will be needed to definitively determine if visuospatial ability differs between the two dementia syndromes.

Surprisingly, no single test from the visuospatial battery reliably distinguished bvFTD from AD other than the pentagons/loops test. The pentagons/loops test was the only measure to demonstrate discriminative potential before covarying for disease severity. Although it's binary score may be oversimplified, it has potential as a useful bedside test to discriminate the two dementia syndromes. Large cohorts with pathological or imaging confirmation are required to determine its positive predictive value and the possible influence from other cognitive domains. The reasons underlying the poor discriminative power of the remaining tasks are likely to be multifactorial. For example, the ACE clock drawing test failed to distinguish between AD and bvFTD, likely due to the test's reliance on intact attention, executive planning, numeric and semantic knowledge, all of which may be compromised in bvFTD [23,63]. The VOSP subtasks, though limited by selection bias, again did not distinguish bvFTD from AD, consistent with at least one study which used the total VOSP score [64]. Whether this reflects contribution from other cognitive domains, or a degree of visuoperception impairment with greater disease progression in bvFTD, remains unknown.

The presence of visuospatial deficits in bvFTD stands in contrast with the current diagnostic criteria which emphasise a relative sparing of visuospatial function [36]. These results, however, may reflect the influence of other cognitive factors on task performance, rather than a core visuospatial deficit per se. Executive deficits, impulsivity, apathy, disinhibition, and impaired attention on task performance all have the potential to affect performance on traditional tests of visuospatial function [17,18,65–67]. Additionally, motor symptoms likely impact performance on drawing tasks [17,23,68,69]. On the other hand, the emergence of visuospatial dysfunction in bvFTD with advancing disease severity cannot be easily discounted, as parietal involvement is evident with disease progression [26,70]. In addition, our large sample of bvFTD patients may have included carriers of the *C9orf72* repeat expansion which have been reported to show parietal atrophy compared with sporadic cases of bvFTD [25]. Specific tests of visuospatial abilities, which circumvent executive and motor confounds, are therefore required to determine the extent to which core visuospatial processes are disrupted in the early stages of bvFTD [71].

A further variable to consider is the influence of disease severity on visuospatial performance. When disease severity was taken into account, AD showed disproportionate visuospatial impairments compared with bvFTD. These deficits arose on the ACE visuospatial subscale, most notably the pentagons/loops (results were consistent across both tasks) and cube copy, as well as the RCF copy task, in keeping with a number of previous studies [41,57,72,73]. Importantly, the discriminative potential of these tasks may stem from their reliance upon constructive processes, characteristically impaired from early on in the AD trajectory [3]. In contrast, tests of visual perception were not found to differentiate between the two dementia groups, with the exception of the cube analysis subtask, likely reflecting the increased complexity of a three-dimensional component and stimulus enumeration [74]. This result is consistent with previous studies [33,73,75,76]. Constructional tasks, especially those based on copying a model, reveal the most prominent deficits in AD patients, likely reflecting early parietal involvement in this disease [31].

Several limitations of the present study should be acknowledged. Firstly, most patients did not undergo PiB-PET or have pathology confirmed at *post-mortem*, and thus our classification is based on clinical and imaging criteria alone. Importantly, however, diagnoses were made at a specialised dementia research centre via consensus between experienced neurologists and neuropsychologists. Additionally, among the patients who underwent PiB-PET imaging, all the results were in keeping with the original clinical diagnosis, pointing to the accuracy of the clinical diagnostic procedure. Second, as with any cohort of bvFTD, presence of patients carrying the *C9orf72* expansion, which has been reported to be associated with greater parietal involvement, cannot be discounted. Undoubtedly, it will be informative to investigate whether levels of visuospatial impairment vary between sporadic and genetic causes of bvFTD.

Despite efforts to match the groups, the bvFTD patients were more functionally impaired than AD, as measured by the FRS. This observation raises the important issue of how best to account for, and indeed control for, disease severity when comparing cognitive performance across different dementia syndromes. The pattern and severity of cognitive and behavioural deficits differ in AD and bvFTD precisely because these syndromes are defined according to distinct predominant clinical features: cognitive in AD and behavioural in bvFTD. Other methods based on cognitive scoring or disease duration are generally biased towards AD and therefore tend to under-represent disease severity in FTD [47]. In keeping with recent studies [15,45–47,54,77,78], we used the FRS in an attempt to address this issue.

In order to control for ageing effects, the bvFTD and AD cohorts were matched for chronological age. Although younger than what is typical for this population, all AD patients presented with predominantly amnestic deficits and therefore aligned with the classification of amnestic AD. Finally, the selective use of the VOSP is a limitation of the study. All data were collected retrospectively from the research clinic. Hypothesis-driven testing was applied at the research clinic when administering the VOSP. When visuoconstructional deficits were detected on the RCF copy task (scoring < 30/36; borderline impairment), the VOSP was administered to establish if basic visuoperceptual difficulties were contributing to the visuoconstructional deficits. As such, our VOSP findings are based on a non-random population which could have potential implications.

In conclusion, traditional neuropsychological tests of visuospatial function demonstrate limited clinical utility in discriminating between AD and bvFTD unless disease severity is taken into account in the analyses. The development of more stringent and challenging visuospatial tasks, incorporating construction and spatial orientation components, and taking disease severity into consideration, will be essential to refine the differential diagnosis of these syndromes. Finally, these new tasks should be used prospectively in a larger range of amyloid and non-amyloid dementias, ideally incorporating PiB-PET or post-mortem

studies, to definitively establish their diagnostic potential.

Conflicts of interest

There are no conflicts of interest present.

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References

[1] T.G. Beach, S.E. Monsell, L.E. Phillips, W. Kukull, Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010, J. Neuropathol. Exp. Neurol. 71 (2012) 266–273, https://doi.org/10.1097/NEN.0b013e31824b211b.

[2] L. Chare, J.R. Hodges, C.E. Leyton, C. McGinley, R.H. Tan, J.J. Kril, et al., New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications, J. Neurol. Neurosurg. Psychiatry 85 (2014) 865–870, https://doi.org/10.1136/jnnp-2013-306948.

[3] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack Jr., C.H. Kawas, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (2011) 263–269, https://doi.org/10.1016/j.jalz.2011.03.005.

[4] C.W. Ritchie, G.M. Terrera, T.J. Quinn, Dementia trials and dementia tribulations: methodological and analytical challenges in dementia research, Alzheimers Res. Ther. 7 (2015) 31, https://doi.org/10.1186/s13195-015-0113-6.

[5] ThinkPlace Pty Ltd., NHMRC Dementia Research and Translation Priority Setting Project: Summary Document, (2015).

[6] B. Dubois, H.H. Feldman, C. Jacova, H. Hampel, J.L. Molinuevo, K. Blennow, et al., Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria, Lancet Neurol. 13 (2014) 614–629, https://doi.org/10.1016/S1474-4422(14)70090-0.

[7] G.D. Rabinovici, W.J. Jagust, Amyloid imaging in aging and dementia: testing the amyloid hypothesis in vivo, Behav. Neurol. 21 (2009) 117–128, https://doi.org/10.3233/BEN-2009-0232.

[8] G. Blessed, B.E. Tomlinson, M. Roth, The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects, Br. J. Psychiatry 114 (1968) 797–811, https://doi.org/10.1192/bjp.114.512.797.

[9] J.R. Burrell, J.R. Hodges, Dementia. Landmark Pap. Neurol, vol. 2015, Oxford University Press, Incorporated, 2015, pp. 289–324.

[10] R.M. Chapman, M. Mapstone, J.W. McCrary, M.N. Gardner, A. Porsteinsson, T.C. Sandoval, et al., Predicting conversion from mild cognitive impairment to Alzheimer's disease using neuropsychological tests and multivariate methods, J. Clin. Exp. Neuropsychol. 33 (2011) 187–199, https://doi.org/10.1080/13803395.2010.499356.

[11] M. Hornberger, O. Piguet, Episodic memory in frontotemporal dementia: a critical review, Brain 135 (2012) 678–692, https://doi.org/10.1093/brain/aws011.

[12] M. Irish, M. Hornberger, S. Lah, L. Miller, G. Pengas, P.J. Nestor, et al., Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease, Neuropsychologia 49 (2011) 2694–2702, https://doi.org/10.1016/j.neuropsychologia.2011.05.017.

[13] M. Irish, O. Piguet, J.R. Hodges, M. Hornberger, Common and unique gray matter correlates of episodic memory dysfunction in frontotemporal dementia and alzheimer's disease, Hum. Brain Mapp. 35 (2014) 1422–1435, https://doi.org/10.1002/hbm.22263.

[14] C. Pennington, J.R. Hodges, M. Hornberger, Neural correlates of episodic memory in Behavioral variant frontotemporal dementia, J. Alzheimers Dis. 24 (2011) 261–268, https://doi.org/10.3233/JAD-2011-101668.

[15] S. Wong, E. Flanagan, G. Savage, J.R. Hodges, M. Hornberger, Contrasting prefrontal cortex contributions to episodic memory dysfunction in behavioural variant Frontotemporal dementia and Alzheimer's disease, PLoS One 9 (2014) e87778, , https://doi.org/10.1371/journal.pone.0087778.

[16] R.L. Buckner, A.Z. Snyder, B.J. Shannon, G. LaRossa, R. Sachs, A.F. Fotenos, et al., Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory, J. Neurosci. 25 (2005) 7709–7717, https://doi.org/10.1523/JNEUROSCI.2177-05.2005.

[17] D.S. Geldmacher, Visuospatial dysfunction in the neurodegenerative diseases, Front. Biosci. J. Virtual. Libr. 8 (2003) e428–e436, https://doi.org/10.2741/1143.

[18] M. Harciarek, K. Jodzio, Neuropsychological differences between frontotemporal dementia and Alzheimer's disease: a review, Neuropsychol. Rev. 15 (2005) 131–145, https://doi.org/10.1007/s11065-005-7093-4.

[19] P.K. Mandal, J. Joshi, S. Saharan, Visuospatial perception: an emerging biomarker for Alzheimer's disease, J. Alzheimers Dis. 31 (2012) S117–S135, https://doi.org/10.3233/JAD-2012-120901.

[20] K.L. Possin, V.R. Laluz, O.Z. Alcantar, B.L. Miller, J.H. Kramer, Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia, Neuropsychologia 49 (2011) 43–48, https://doi.org/10.1016/j.neuropsychologia.2010.10.026.

[21] R.A. Sperling, P.S. LaViolette, K. O'Keefe, J. O'Brien, D.M. Rentz, M. Pihlajamaki, et al., Amyloid deposition is associated with impaired default network function in older persons without dementia, Neuron 63 (2009) 178–188, https://doi.org/10.1016/j.neuron.2009.07.003.

[22] J.J. Kril, V. Macdonald, S. Patel, F. Png, G.M. Halliday, Distribution of brain atrophy in behavioral variant frontotemporal dementia, J. Neurol. Sci. 232 (2005) 83–90, https://doi.org/10.1016/j.jns.2005.02.003.

[23] O. Piguet, M. Hornberger, E. Mioshi, J.R. Hodges, Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management, Lancet Neurol. 10 (2011) 162–172, https://doi.org/10.1016/S1474-4422(10)70299-4.

[24] C. Dobson-Stone, M. Hallup, L. Bartley, C.E. Shepherd, G.M. Halliday, P. Schofield, et al., C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts, Neurology 79 (2012) 995–1001, https://doi.org/10.1212/WNL.0b013e3182684634.

[25] M. Irish, E. Devenney, S. Wong, C. Dobson-Stone, J.B. Kwok, O. Piguet, et al., Neural substrates of episodic memory dysfunction in behavioural variant frontotemporal dementia with and without C9ORF72 expansions, NeuroImage Clin. 2 (2013) 836–843, https://doi.org/10.1016/j.nicl.2013.06.005.

[26] R. Landin-Romero, F. Kumfor, C.E. Leyton, M. Irish, J.R. Hodges, O. Piguet, Disease-specific patterns of cortical and subcortical degeneration in a longitudinal study of Alzheimer's disease and behavioural-variant frontotemporal dementia, NeuroImage 151 (2017) 72–80, https://doi.org/10.1016/j.neuroimage.2016.03.032.

[27] J.L. Whitwell, S.A. Przybelski, S.D. Weigand, R.J. Ivnik, P. Vemuri, J.L. Gunter, et al., Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study, Brain 132 (2009) 2932–2946, https://doi.org/10.1093/brain/awp232.

[28] T. Iachini, A. Iavarone, V.P. Senese, F. Ruotolo, G. Ruggiero, Visuospatial memory in healthy elderly, AD and MCI: a review, Curr. Aging Sci. 2 (2009) 43–59.

[29] P. Tiraboschi, D.P. Salmon, L.A. Hansen, R.C. Hofstetter, L.J. Thal, J. Corey-Bloom, What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 129 (2006) 729–735, https://doi.org/10.1093/brain/awh725.

[30] H.I.L. Jacobs, M.P.J. Van Boxtel, J. Jolles, F.R.J. Verhey, H.B.M. Uylings, Parietal cortex matters in Alzheimer's disease: an overview of structural, functional and metabolic findings, Neurosci. Biobehav. Rev. 36 (2012) 297–309, https://doi.org/10.1016/j.neubiorev.2011.06.009.

[31] P.J. Nestor, T.D. Fryer, J.R. Hodges, Declarative memory impairments in Alzheimer's disease and semantic dementia, NeuroImage 30 (2006) 1010–1020, https://doi.org/10.1016/j.neuroimage.2005.10.008.

[32] G. Pengas, K. Patterson, R.J. Arnold, C.M. Bird, N. Burgess, P.J. Nestor, Lost and found: bespoke memory testing for Alzheimer's disease and semantic dementia, J. Alzheimers Dis. 21 (2010) 1347–1365, https://doi.org/10.3233/JAD-2010-100654.

[33] S. Siri, I. Benaglio, A. Frigerio, G. Binetti, S.F. Cappa, A brief neuropsychological assessment for the differential diagnosis between frontotemporal dementia and Alzheimer's disease, Eur. J. Neurol. 8 (2001) 125–132, https://doi.org/10.1046/j.1468-1331.2001.00179.x.

[34] M. Blair, A. Kertesz, P. Mcmonagle, W. Davidson, N. Bodi, Quantitative and qualitative analyses of clock drawing in frontotemporal dementia and Alzheimer's disease, J. Int. Neuropsychol. Soc. 12 (2006) 159–165, https://doi.org/10.1017/S1355617706060255.

[35] R. Moretti, P. Torre, R.M. Antonello, G. Cazzato, A. Bava, Ten-point clock test: a correlation analysis with other neuropsychological tests in dementia, Int. J. Geriatr. Psychiatry 17 (2002) 347–353, https://doi.org/10.1002/gps.600.

[36] K. Rascovsky, J.R. Hodges, D. Knopman, M.F. Mendez, J.H. Kramer, J. Neuhaus, et al., Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, Brain 134 (2011) 2456–2477, https://doi.org/10.1093/brain/awr179.

[37] S. Tu, S. Wong, J.R. Hodges, M. Irish, O. Piguet, M. Hornberger, Lost in spatial translation – a novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia, Cortex 67 (2015) 83–94, https://doi.org/10.1016/j.cortex.2015.03.016.

[38] R. Mathew, T.H. Bak, J.R. Hodges, Diagnostic criteria for corticobasal syndrome: a comparative study, J. Neurol. Neurosurg. Psychiatry (2011), https://doi.org/10.1136/jnnp-2011-300875 jnnp-2011-300875.

[39] M.L. Gorno-Tempini, A.E. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S.F. Cappa, et al., Classification of primary progressive aphasia and its variants, Neurology 76 (2011) 1006–1014, https://doi.org/10.1212/WNL.0b013e31821103e6.

[40] S.J. Crutch, J.M. Schott, G.D. Rabinovici, M. Murray, J.S. Snowden, Flier W.M. van der, et al., Consensus classification of posterior cortical atrophy, Alzheimers Dement. J. Alzheimers Assoc. 13 (2017) 870–884, https://doi.org/10.1016/j.jalz.2017.01.014.

[41] S. Hsieh, S. Schubert, C. Hoon, E. Mioshi, J.R. Hodges, Validation of the

Addenbrooke's cognitive examination III in frontotemporal dementia and Alzheimer's disease, Dement. Geriatr. Cogn. Disord. 36 (2013) 242–250, https://doi.org/10.1159/000351671.
[42] E. Mioshi, K. Dawson, J. Mitchell, R. Arnold, J.R. Hodges, The Addenbrooke's cognitive examination revised (ACE-R): a brief cognitive test battery for dementia screening, Int. J. Geriatr. Psychiatry 21 (2006) 1078–1085, https://doi.org/10.1002/gps.1610.
[43] M. So, D. Foxe, F. Kumfor, C. Murray, S. Hsieh, G. Savage, et al., Addenbrooke's cognitive examination III: psychometric characteristics and relations to functional ability in dementia, J. Int. Neuropsychol. Soc. 24 (2018) 854–863, https://doi.org/10.1017/S1355617718000541.
[44] P.S. Mathuranath, P.J. Nestor, G.E. Berrios, W. Rakowicz, J.R. Hodges, A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia, Neurology 55 (2000) 1613–1620, https://doi.org/10.1212/01.wnl.0000434309.85312.19.
[45] E. Mioshi, S. Hsieh, S. Savage, M. Hornberger, J.R. Hodges, Clinical staging and disease progression in frontotemporal dementia, Neurology 74 (2010) 1591–1597, https://doi.org/10.1212/WNL.0b013e3181e04070.
[38] R. Mathew, T.H. Bak, J.R. Hodges, Diagnostic criteria for corticobasal syndrome: a comparative study, J. Neurol. Neurosurg. Psychiatry (2011), https://doi.org/10.1136/jnnp-2011-300875 jnnp-2011-300875.
[47] T.B. Lima-Silva, V.S. Bahia, M.A. Cecchini, L. Cassimiro, H.C. Guimarães, L.B. Gambogi, et al., Validity and Reliability of the Frontotemporal Dementia Rating Scale (FTD-FRS) for the Progression and Staging of Dementia in Brazilian Patients, (2018), https://doi.org/10.1097/WAD.0000000000000246.
[48] A. Rey, Rey-Osterrieth complex figure test, Psychol. Assess. Resour. 30 (1944) 206–356.
[49] E.K. Warrington, M. James, The Visual Object and Space Perception Battery, (1991).
[50] G.D. Rabinovici, A.J. Furst, J.P. O'Neil, C.A. Racine, E.C. Mormino, S.L. Baker, et al., 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration, Neurology 68 (2007) 1205–1212, https://doi.org/10.1212/01.wnl.0000259035.98480.ed.
[51] J.R. Burrell, M. Hornberger, V.L. Villemagne, C.C. Rowe, J.R. Hodges, Clinical profile of PiB-positive corticobasal syndrome, PLoS One 8 (2013) e61025, , https://doi.org/10.1371/journal.pone.0061025.
[52] C.C. Rowe, K.A. Ellis, M. Rimajova, P. Bourgeat, K.E. Pike, G. Jones, et al., Amyloid imaging results from the Australian imaging, biomarkers and lifestyle (AIBL) study of aging, Neurobiol. Aging 31 (2010) 1275–1283, https://doi.org/10.1016/j.neurobiolaging.2010.04.007.
[53] V.L. Villemagne, K.E. Pike, G. Chételat, K.A. Ellis, R.S. Mulligan, P. Bourgeat, et al., Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease, Ann. Neurol. 69 (2011) 181–192, https://doi.org/10.1002/ana.22248.
[54] E. Mioshi, D. Foxe, F. Leslie, S. Savage, S. Hsieh, L. Miller, et al., The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease, Alzheimer Dis. Assoc. Disord. 27 (2013) 68–73.
[55] D. Foxe, C.E. Leyton, J.R. Hodges, J.R. Burrell, M. Irish, O. Piguet, The neural correlates of auditory and visuospatial span in logopenic progressive aphasia and Alzheimer's disease, Cortex 83 (2016) 39–50, https://doi.org/10.1016/j.cortex.2016.07.003.
[56] F. Kumfor, M. Irish, J.R. Hodges, O. Piguet, Discrete neural correlates for the recognition of negative emotions: insights from frontotemporal dementia, PLoS One 8 (2013) e67457, , https://doi.org/10.1371/journal.pone.0067457.
[57] N.A. Pachana, K.B. Boone, B.L. Miller, J.L. Cummings, N. Berman, Comparison of neuropsychological functioning in Alzheimer's disease and frontotemporal dementia, J. Int. Neuropsychol. Soc. 2 (1996) 505–510, https://doi.org/10.1017/S1355617700001673.
[58] C.L. Stopford, J.C. Thompson, D. Neary, A.M.T. Richardson, J.S. Snowden, Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia, Cortex 48 (2012) 429–446, https://doi.org/10.1016/j.cortex.2010.12.002.
[59] E. Devenney, L. Bartley, C. Hoon, C. O'Callaghan, F. Kumfor, M. Hornberger, et al., Progression in behavioral variant frontotemporal dementia: a longitudinal study, JAMA Neurol. 72 (2015) 1501–1509, https://doi.org/10.1001/jamaneurol.2015.2061.
[60] M. Elamin, G. Holloway, T.H. Bak, S. Pal, The utility of the Addenbrooke's cognitive examination version three in early-onset dementia, Dement. Geriatr. Cogn. Disord. 41 (2016) 9–15, https://doi.org/10.1159/000439248.
[61] M. Irish, J.R. Hodges, O. Piguet, Right anterior temporal lobe dysfunction underlies theory of mind impairments in semantic dementia, Brain 137 (2014) 1241–1253, https://doi.org/10.1093/brain/awu003.
[62] S. Schubert, C.E. Leyton, J.R. Hodges, O. Piguet, Longitudinal memory profiles in Behavioral-variant frontotemporal dementia and Alzheimer's disease, J. Alzheimers Dis. 51 (2016) 775–782, https://doi.org/10.3233/JAD-150802.
[63] K.I. Shulman, Clock-drawing: is it the ideal cognitive screening test? Int. J. Geriatr. Psychiatry 15 (2000) 548–561, https://doi.org/10.1002/1099-1166(200006)15:6<548::AID-GPS242>3.0.CO;2-U.
[64] C.J. Mahoney, G.R. Ridgway, I.B. Malone, L.E. Downey, J. Beck, K.M. Kinnunen, et al., Profiles of white matter tract pathology in frontotemporal dementia, Hum. Brain Mapp. 35 (2014) 4163–4179, https://doi.org/10.1002/hbm.22468.
[65] P.J. Eslinger, P. Moore, S. Antani, C. Anderson, M. Grossman, Apathy in frontotemporal dementia: behavioral and neuroimaging correlates, Behav. Neurol. (2012), https://doi.org/10.3233/BEN-2011-0351.
[66] D. Quaranta, C. Marra, C. Rossi, G. Gainotti, C. Masullo, Different apathy profile in behavioral variant of frontotemporal dementia and Alzheimer's disease: a preliminary investigation, Curr. Gerontol. Geriatr. Res. 2012 (2012), https://doi.org/10.1155/2012/719250.
[67] D.P. Salmon, M.W. Bondi, Neuropsychological assessment of dementia, Annu. Rev. Psychol. 60 (2009) 257–282, https://doi.org/10.1146/annurev.psych.57.102904.190024.
[68] N.B.M. Quental, S.M.D. Brucki, O.F.A. Bueno, Visuospatial function in early Alzheimer's disease, Dement. Neuropsychol. 3 (2009) 234–240.
[69] N.B.M. Quental, S.M.D. Brucki, O.F.A. Bueno, Visuospatial function in early Alzheimer's disease—the use of the visual object and space perception (VOSP) battery, PLoS One 8 (2013) e68398.
[70] M. Irish, R. Landin-Romero, A. Mothakunnel, S. Ramanan, S. Hsieh, J.R. Hodges, et al., Evolution of autobiographical memory impairments in Alzheimer's disease and frontotemporal dementia – a longitudinal neuroimaging study, Neuropsychologia (2018), https://doi.org/10.1016/j.neuropsychologia.2017.03.014.
[71] S. Salimi, M. Irish, D. Foxe, J.R. Hodges, O. Piguet, J.R. Burrell, Can visuospatial measures improve the diagnosis of Alzheimer's disease? Alzheimers Dement. Diagn. Assess. Dis. Monit. 10 (2018) 66–74, https://doi.org/10.1016/j.dadm.2017.10.004.
[72] J.H. Kramer, J. Jurik, S.J. Sha, K.P. Rankin, H.J. Rosen, J.K. Johnson, et al., Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease, Cogn. Behav. Neurol. 16 (2003) 211–218.
[73] M.C. Tartaglia, Y. Zhang, C. Racine, V. Laluz, J. Neuhaus, L. Chao, et al., Executive dysfunction in frontotemporal dementia is related to abnormalities in frontal white matter tracts, J. Neurol. 259 (2012) 1071–1080, https://doi.org/10.1007/s00415-011-6300-x.
[74] L.J. Rapport, S.R. Millis, P.J. Bonello, Validation of the Warrington theory of visual processing and the visual object and space perception battery, J. Clin. Exp. Neuropsychol. 20 (1998) 211–220, https://doi.org/10.1076/jcen.20.2.211.1169.
[75] D. Grossi, N.A. Fragassi, L. Chiacchio, L. Valoroso, R. Tuccillo, C. Perrotta, et al., Do visuospatial and constructional disturbances differentiate frontal variant of frontotemporal dementia and Alzheimer's disease? An experimental study of a clinical belief, Int. J. Geriatr. Psychiatry 17 (2002) 641–648, https://doi.org/10.1002/gps.654.
[76] J.R. Hodges, K. Patterson, R. Ward, P. Garrard, T. Bak, R. Perry, et al., The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study, Neuropsychology 13 (1999) 31–40, https://doi.org/10.1037/0894-4105.13.1.31.
[77] N. Dermody, S. Wong, R. Ahmed, O. Piguet, J.R. Hodges, M. Irish, Uncovering the neural bases of cognitive and affective empathy deficits in Alzheimer's disease and the behavioral-variant of frontotemporal dementia, J. Alzheimers Dis. 53 (2016) 801–816, https://doi.org/10.3233/JAD-160175.
[78] L. Frings, B. Yew, E. Flanagan, B.Y.K. Lam, M. Hüll, H.-J. Huppertz, et al., Longitudinal grey and white matter changes in frontotemporal dementia and Alzheimer's disease, PLoS One 9 (2014) e90814, , https://doi.org/10.1371/journal.pone.0090814.